Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IL05/000140

International filing date: 04 February 2005 (04.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/604,615
Filing date: 25 August 2004 (25.08.2004)

Date of receipt at the International Bureau: 09 May 2005 (09.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

PCT/IL2005/000140
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APPLICATION NUMBER: ***60/604,615***
FILING DATE: ***August 25, 2004***

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

22464 U.S.PTO 60/604615 082504

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TITLE OF THE INVENTION (280 characters max)

MOTOR REHABILITATION WITH BRAIN PLASTICITY

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages*	24, incl. 7 drawing figures	☐ CD(s), Number	
☐ Drawing(s) *Number of Sheets*		☐ Other (specify)	
☐ Application Data Sheet. See 37 CFR 1.76			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ Applicant claims small entity status. See 37 CFR 1.27.		FILING FEE AMOUNT ($)
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE

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Date 08/25/2004

REGISTRATION NO. *(if appropriate)* 41,016

Docket Number: 414/04188

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Applicant:	Omer Einav et al.
Serial No:	To Be Assigned
Filing Date:	August 25, 2004, herewith
For:	MOTOR REHABILITATION WITH BRAIN PLASTICITY
Enclosures:	(1) Provisional Application Cover Sheet (in duplicate); (2) Specification including seven drawing figures (24 pages); (3) Acknowledgement Postcard.

MOTOR REHABILITATION WITH BRAIN PLASTICITY

RELATED APPLICATIONS

This application claims the benefit under §119(e) of U.S. Provisional Application No. 60/542,022, filed on February 5, 2004, titled "Methods and Apparatus for Rehabilitation and Training", U.S. Provisional Application No. 60/566,079, filed on April 29, 2004, titled "Fine Motor Control Rehabilitation", and U.S. Provisional Application No. 60/566,078, filed on April 29, 2004, titled "Neuromuscular Stimulation", the disclosures of all of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention is related to the field of rehabilitation, for example utilizing brain activity measurements.

BACKGROUND OF THE INVENTION

Following is a short introduction to measurement of some types of electrical brain activity associated with motor control.

Movement-Associated Cortical Potential (MAC) Accompanying Voluntary Movement

Experiments have shown that every voluntary movement is associated with an electrical cortical potential that can be recorded over the scalp. This activity is typically characterized by three components:

1. The "Bereitschaftspotential" (**BP**) or "Readiness Potential" defined as a slowly 'rising' negative potential that occurs 1-2 seconds prior to volitional self-initiated movements. It is related to the preparatory process prior to limb movement.

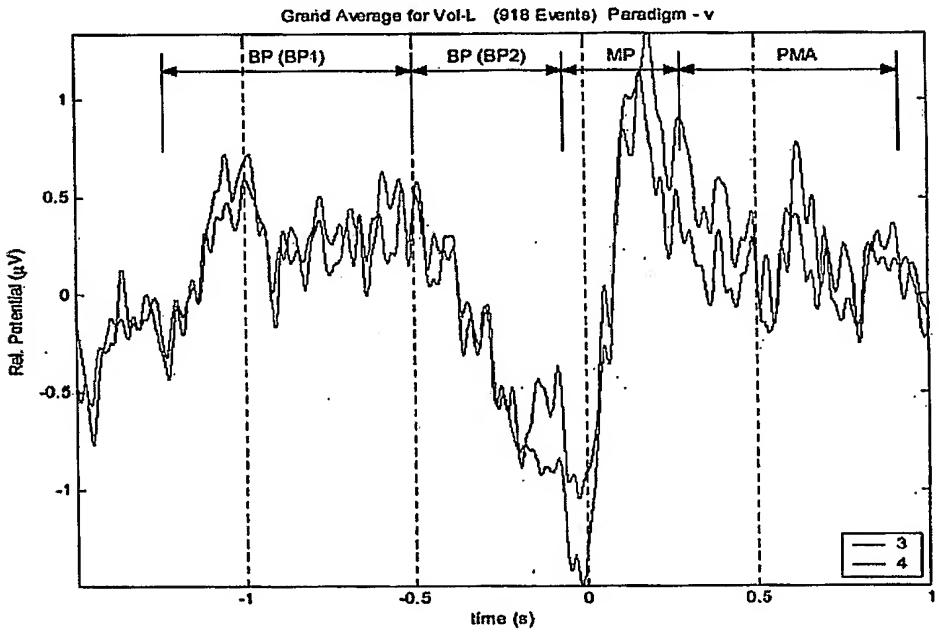
This BP consists in fact of two components:

- an early component (BP1) that lasts from the very beginning of the BP (starting 1-2s or more prior to movement onset depending on the complexity of the movement) to approximately 0.5s before movement onset; and
- a late component (BP2) that occurs for the last half second before onset (see Figure 1). BP2 has a steeper negative slope than BP1.

2. The motor potential (**MP**) which consists of an initial sharp negative deflection that follows the BP's more gradual negativity. This potential is related to motor activity. At movement onset (at t=0 as shown in the Figure 1 below), there exists a sharp positive inflection that peaks at around 200ms after the movement onset. This period is typically contaminated with EMG artifacts.

3. The post-movement activity (PMA) which is the potential change (starting after 200ms after the movement onset) whereby the brain resynchronizes and resumes 'normal' activity.

Figure 1 presents an averaged Motor Related Potential template that illustrates these distinguishable periods. This in an example of an averaged MRP recorded for 918 left finger movement trials (onset at t=0) at C3 (channel 3) and C4 (channel 4, lighter grey, higher peak).



For unilateral movement, BP1 has a symmetric and bilateral topography on the scalp i.e. it is not lateralized about the motor cortex.

In contrast BP2 is larger (more negative) over the primary motor area of the contra lateral hemisphere. This is evident in Figure 1 for the last ~200 ms prior to finger press at time t=0. The electrode C4 is positioned on the right side of the head and for the left finger movement as shown exhibits a more negative potential on average than the contra-laterally placed C3 electrode.

Rich experimental evidence indicates that BP1 and BP2 might involve different functional systems. Experiments in PET (Positron Emission) and unicellular recordings in monkeys suggested that parts of the mesial frontal cortex, and typically the Supplemental Motor Area, may be involved in the generation of BP1. On the other hand, several investigators concluded that BP2 potential reflects expression of nerve excitation, namely, activity of cortical-spinal tract concerning efferent discharges of pyramidal tract.

In recent years, the Readiness Potential has been the subject of a debate. When subjects were requested to recall which spatial "clock-position" a revolving spot occupied at the time

they first became aware of intending to execute a self-paced movement, the moment indicated did not coincide with the beginning of the slow wave, but occurred about 500 ms later. The conclusion is that the awareness of willingness to move occurred later than the beginning of the electrophysiological event and that, consequently, the first part of the decision process to move was infra-conscious.

All the above supports the fundamental EEG theory that potential negativity can be related to activity of the cortical areas whereas positivity is related to inactivity. Since the extremities of the human body are controlled by the contra lateral side of the brain it stands to reason that there should be more activity and hence 'negativity' on the contra lateral side.

In summary, the signal distribution over the scalp of the BP2 potential shows maximum at C3, (central left scalp), in case of voluntary right upper arm flexion movement. The maximum was at C4, (central right scalp), in case of voluntary left upper arm flexion movement. The distribution of the late PMA potential showed maximum at Cz, (central medial in case of voluntary right or left upper arm flexion movement. The only part of the MAC that shows potentials contra lateral to the side of the movement is BP2.

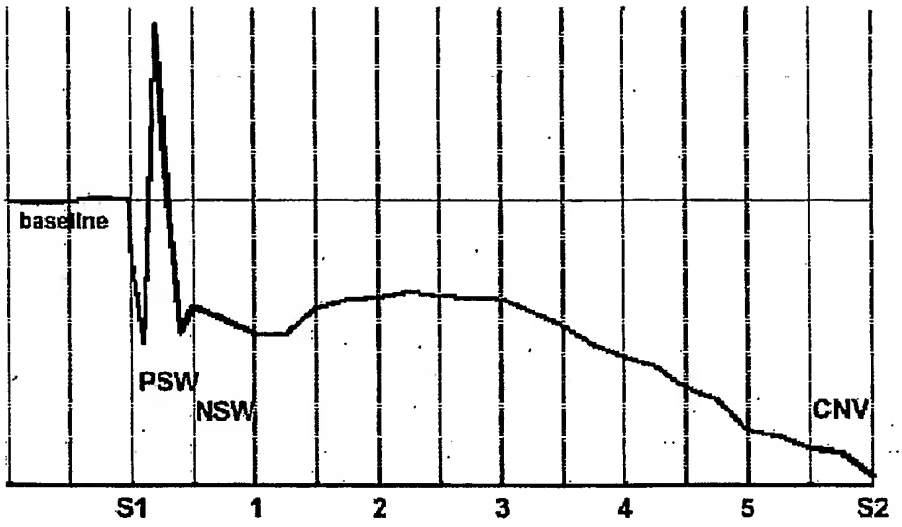
Contingent Negative Variation

In some experimental setups the generation of a MAC potential involves the performance of a prescribed task under the prompting of a pair of cuing stimuli: S1 and S2, separated by a given time interval. The first cue, (S1), is a 'warning' or 'preparatory' cue which is subsequently followed by a second 'imperative' cue (S2).

The subject is instructed to perform the given task as fast as possible following the presentation of the imperative stimulus (S2). Briefly, the preparatory stimulus precedes the imperative and thus acts as a 'get ready' signal to warn the subject that the imperative stimulus is approaching.

Under these conditions, the resultant waveform recorded over the scalp is a slow negative shift beginning at the presentation of S1 and ending roughly at the presentation of S2.

Figure 2 shows a typical event-related potential in an S1-S2 paradigm, measured from central derivations (average of C3 and C4). The x-axis shows the presentations of S1 (onset at time t = 0), and S2 (onset at t = 6 seconds). The measures for PSW, NSW, and CNV as used in the present study are indicated.



The task can be, for instance, that S1 is a sound which the subject had to decide if it belongs to a previously memorized set of sounds. The result of this memory search task indicates the response instruction expected at S2; for instance, that a response has to be given either with the left or with the right hand.

Figure 2 shows a typical event-related potential, developing in the S1-S2 interval. Within the first second after S1 a slow wave complex can be seen which consists of a **positive (slow wave) deflection** (the **"PSW"**).

Later in the S1-S2 interval, a slow negative shift develops, which reaches a maximum immediately before S2. This shift is called the **contingent negative variation (CNV).**

When the S1-S2 interval is sufficiently long, three seconds or more, the negative shift clearly consists of two parts. The first part, called **negative slow wave (NSW),** is maximal at the frontal positions, between about 0.5 and 1 second after S1.

PSW has a parietal dominance and is assumed to reflect the outcome of stimulus evaluation and has been found to attenuate when the task is more difficult.

NSW has a frontal maximum, and some authors have found that is lateralized in the right hemisphere. It is often regarded as part of the **orientation reaction,** because it is affected by the physical characteristics of S1, such as intensity, probability, and modality. The NSW is larger when the task at S1 is more difficult.

The **CNV** is mainly related to **motor response preparation;** its amplitude depends heavily on the task demands at S2, and is affected by task variables as speed/accuracy

instructions, and the duration of the S1-S2 interval. CNV has the largest amplitude at the central electrodes.

CNV and Readiness Potential

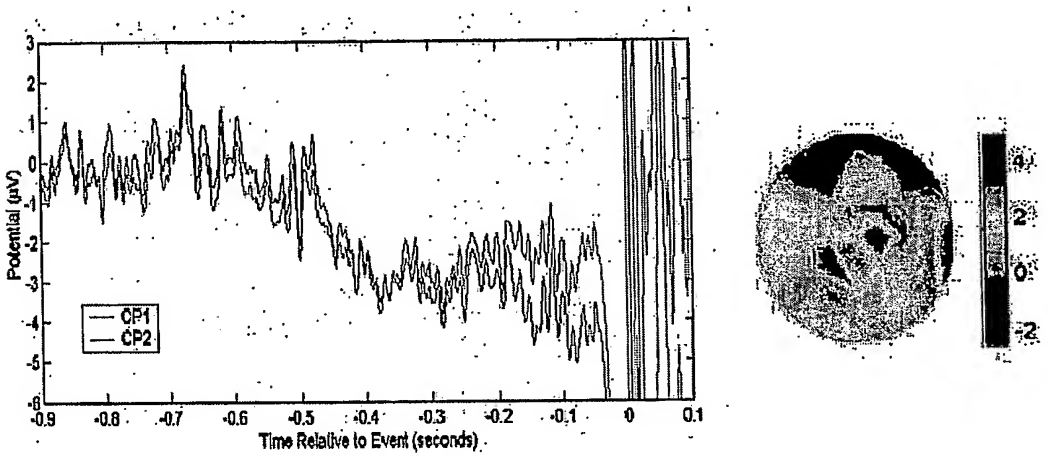
CNV and BP are often considered to reflect the same process, since they are maximal at the same positions on the scalp, and immediately before a response is given. The difference between CNV and RP is, however, that the first is derived as a stimulus-locked potential, whereas the latter is derived relative to the response.

Whereas the BP is specific to motor readiness, and is concentrated over the primary motor cortex, the CNV is associated with more cognitive aspects of anticipation, and is generally localized to frontal and frontal-central cortex.

Topographic Plots of Bereitschafts Amplitudes with different types of Movement

In order to get a good picture of overall Motor Related Potential distribution effects, including lateralization effects, experimenters employ a two dimensional interpolation scheme from data collected through a multiple electrode arrangements. This technique facilitates the visualization of the topographic distribution of BP amplitudes over the entire scalp surface. (Briefly the data processing method consists of: first, the amplitude of the total negativity is measured algorithmically for each electrode position of the whole scalp arrangement. Because the data includes a large amount of high-frequency noise, a **mean of 20-50ms** of voltage data is used to estimate the potential at the start and end of each BP waveform. The end value is then subtracted from the start value, thus yielding (in most cases) a positive magnitude for the negativity. These data is then combined with the known relative coordinates of each electrode to generate a two-dimensional grid interpolation of the overall negativity values. In addition, before the interpolation is applied, the EOG and EMG electrodes are removed from the data set as their given coordinates are figurative and they furthermore showed no evidence of significant waveforms.)

Free Movement: If subjects are asked to initiate a voluntary extension of the middle and ring fingers necessary and sufficient for production of a reliable Extensor Communis EMG signal of the right hand only, the recorded MAC is as in Figure 3 (left) and the topographic distribution of the signal following the data processing described above is as in Figure 3 (right).



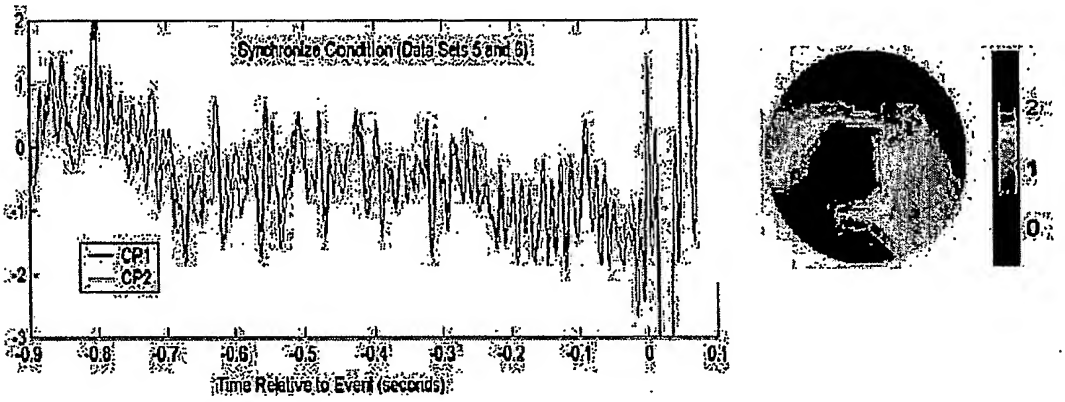
The figure is originally in color, with the color scale being red (4), yellow (2), turquoise (0) and blue (-2). CP2 (central parietal 2, slightly to the right of the central line and just below (towards the back of the brain, relative to the point in Figure 1) is lighter than CP1 in the topographical map. Also, in the graph on the left side of Figure 3, CP2 is higher in the right side of the graph and lower in the left side of the graph , as compared to CP1. (Note: in this case the blue line (CP1) in the graph in Fig.3 left shows the activity contra lateral to the movement)

In this case the voluntary movements are completely at the will of the participant, although a rough guideline is given to leave at least two to three seconds between movements. Accordingly, we can see most of the features described previously.

Applying the algorithm we can see that there are two spots of maximal amplitude of the whole signal: one is central and the other is slightly to the side contra lateral to the movement.

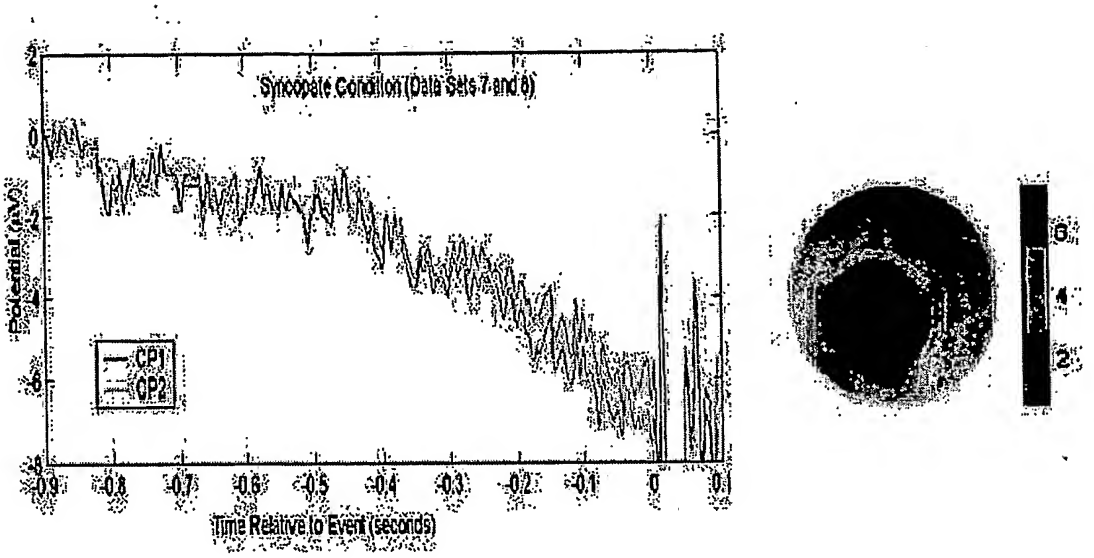
Synchronized Movement: If instead of moving the finger at will the subject is to initiate movement according to a self-maintained, even, metrical pulse with a rough guideline frequency of around 0.5Hz, the results are different. Ideally this will produce MAC events at the steady, regular rate of 0.5Hz. These events should be phase locked to the subject's internal pulse. This is a 'synchronize' condition.

The resulting topographical maps are shown in Figure 4 where BP amplitude is visualized as a color spectrum mapping (shown as grey scale). In these plots, a clear distribution effect of the experimental condition is even more evident than in the previous case of free movement.



In this second case the subject was instructed to initiate movement according to a self-maintained, even, metrical pulse with a rough guideline frequency of around 0.5Hz. As before, the movement consisted in the extension of the middle and ring fingers of the right hand sufficient for production of a reliable Extensor Communis EMG signal. It is clear that in this condition, the spread is mostly towards the left side of the head.

Syncopate movement: In this third condition, the subject is again instructed to maintain an internal metrical pulse. However, in this trial the subject is instructed to initiate finger movements exactly **counter** to the pulse. That is, the movements should be phase shifted by half a period from the maintained internal pulse. Ideally this will produce MAC vents at a frequency of 0.5, phase-shifted by 1 second from the internal pulse. This is the 'syncopate' condition. Results are shown in Figure 5.



From the last three figures it can be seen that a clear distribution of the experimental condition is evident. First, there is an apparent spreading in the location of maximum BP amplitude in all the experimental conditions relative to the "Free Movement" condition. In the "Synchronized" conditions, the spread is mostly towards the left side of the head. In the "Syncopate" condition some spread to the right side is also present.

One potential effect is the appearance of CNV in the syncopate conditions. As described in a previous section, CNV usually marks expectation or anticipation in non-motor regimes.

Motor imagery as activator of cortical activation

Very recently a technique named "mirror therapy" has been reported to be used to activate unused cortical networks and help to reduce the pain associated with cortical abnormalities following injury like in phantom pain and stroke. Briefly, "mirror therapy" involves the movement of a limb inside a mirror box such that visual feedback of the affected hand is replaced by that of the (reflected) unaffected hand. There is therefore an attempt to reconcile motor output and sensory feedback and to activate pre-motor cortices. In his last article, Moseley 2004 writes: "The mechanism of the healing effect of this technique, although not clear, may involve the sequential activation of cortical pre-motor and motor networks, or sustained and focused attention to the affected limb, or both."

SUMMARY OF THE INVENTION

An aspect of some embodiments of the invention relates to robot-assisted rehabilitation which utilizes EEG measurements. In one exemplary embodiment of the invention, the

bilateral Readiness Potential is monitored, quantified and/or displayed prior to a precise movement path, (e.g., provided by a robot), in order to induce, monitor, entrain and/or assess plastic changes in the brain.

In an exemplary embodiment of the invention, a robotic manipulator, for example an apparatus as described in US provisional application 60/542,022, is used. This apparatus can include an optional display, an optional processor, an optional user input and a robotic manipulation portion or a resistive portion. In some embodiments described therein, the device can be configured for one or more of causing a set motion, resisting motion, copying motion between limbs (e.g., hands, arms, feet or legs), assisting motion of a limb and performing motion of multiple joints. In addition, such a manipulator can also measure limb positions and forces or these can be measured in other ways. The use of a processor and an input can allow more detailed programming.

Additional useful apparatus is described in US provisional application 60/566,078, the disclosure of which is incorporated herein by reference, in which EMG measurement in a healthy limb are used for controlling the rehabilitation and/or stimulation of an unhealthy limb. There are optionally four EMG channels, one channel measuring EMG signals from each of four muscles: the biceps, the triceps, the flexors, and the extensors. Each channel uses three electrodes, two recording signals from near each end of the muscle, and one reference electrode in the middle. In that application, a low level signal based on the measured EMG in the healthy limb was applied to the paretic limb, to assist in motion, to provide feedback to the patient and/or to provide encouragement.

In an exemplary embodiment of the invention, the capabilities of a robot manipulator for movement planning, programming, precise repetition, and/or an optional high degree of synchronization with the MAC monitoring, allow for total or more total control over one or more important factors having to do with rehabilitation.

In an exemplary embodiment of the invention, it is assumed that a common characteristic of endogenous components, (based on an internal assessment process) is the dependence on attention. Whereas exogenous components tend to persist under varying degrees of attentiveness towards the event, an endogenous event is often augmented under increased attention or extinguished in the presence of distracting stimuli. Optionally, a measurement of the depth of CNV or BP can reflect the attentive strength during rehabilitation.

In an exemplary embodiment of the invention, the apparatus provides various repetitive synchronized schedules of motion, which are used to monitor and/or improve cortical activation associated with it.

In an exemplary embodiment of the invention, the apparatus is used to quantify and/or assess progress of cortical activation skill for example as associated with a repeatable movement schedule.

In an exemplary embodiment of the invention, the apparatus is used to generally activate cortical networks previously dormant.

In an exemplary embodiment of the invention, the apparatus is used to promote synchronization between cortical activation and its associated peripheral result, possibly reconciling motor output with sensory feedback.

In an exemplary embodiment of the invention, the apparatus is used to assess rehabilitation progress as practically related to improvement in cortical activation and, (possibly indirectly), plastic redistribution and progress.

In an exemplary embodiment of the invention, one or more different types of motion (e.g., Free, Synchronized, Syncopated) are tried with a patient and (e.g., on the basis of the degree of cortical activation related with each one of them) their relative effectiveness for rehabilitation are estimated. Optionally, the rate of progression in synchronization of activation and/or in other parameters of cortical activities (e.g., as compared to healthy subjects or motion of healthy limbs), is used to estimate rehabilitation time and/or expected milestones. In an exemplary embodiment of the invention, one or more templates of progression of cortical activity and/or their association with physical rehabilitation are stored and compared to actual progress of a patient. Optionally, a classification of the rehabilitation type is provided based on the type of progress and/or interaction between robot manipulation and cortical activity. Such classification can be a sub-classification of a basic classification based on brain damage.

In an exemplary embodiment of the invention, the detection of repeated signals is used to indicate that a correct brain activity is taking place.

In an exemplary embodiment of the invention, an apparatus is used for providing multiple ways of activating a motor pathway, including one or more of: from higher brain centers (planning), from lower brain centers (feedback of forced motion), from lateral brain center (copying of motion of laterally opposite limb). In an exemplary embodiment of the invention, such multiple ways of activating may serve to assist a patient in overcoming a disability and/or discovering alternative pathways.

In an exemplary embodiment of the invention, it is believed that when there is a temporal and physiological linkage between the planning of a movement (BP), the subsequent execution of that movement by a paretic arm (even when such a movement is largely or completely generated artificially, e.g. using a robot or by the sEMGs of muscles of the contra-lateral arm), the kinesthetic perception of such a movement via sensorial fibers that may be intact, the actual witnessing of the movement taking place at the physiologically expected time after the resolution to start it, and/or the possibility to accurately return to all the above steps time and time again (e.g., with a robotic manipulator); the possibility of positive plastic change to recover mobility is facilitated and/or enhanced. Alternatively or additionally, the above is used for testing and/or assessment.

In an exemplary embodiment of the invention, it is assumed that combined peripheral nerve and brain stimulation ("dual stimulation") induces changes, for example of excitability of normal motor cortex. Alternatively or additionally, it is assumed that "dual stimulation" induces motor cortex plasticity and associated functional improvements. Some basis for this may be found in (Uy J, Ridding MC, Hillier S, Thompson PD, Miles TS. : Does induction of plastic change in motor cortex improve leg function after stroke? Neurology. 2003 Oct 14;61(7):982-4.), the disclosure of which is incorporated herein by reference.

In an exemplary embodiment of the invention, a robot manipulator provides a cuing structure to mimic the syncopate condition described above.

An aspect of some embodiments of the invention relates to using a robotic manipulation system (e.g., active or passive) for diagnosis. In an exemplary embodiment of the invention, the system is used to perform different manipulations and/or complexity levels in a way which will (should) either cause expected brain activation patterns or require the use of certain brain areas. For example, asking a patient to repeat a complex motion exemplified by the system will activate brain areas differently from asking a patient to maintain a constant velocity of motion in a circle under a condition of varying resistance. In another example, more complex motions may require a greater planning effort.

An aspect of some embodiments of the invention relates to assessment of plasticity. In an exemplary embodiment of the invention, the system is used for assessment of plasticity and/or progress and/or efficacy of a rehabilitation treatment. In an exemplary embodiment of the invention, the system provides a same set of repeated exercises, for example, repeated during a same session (to assess intra-session improvement and provide one measure of brain plasticity) or in different sessions (to assess progress between sessions). It should be noted that a

controlled system can control one or more of: the required motion, measurement of variations, timing, graduated changes and/or provide variations in order of exercises. Some of these features may be available using manual methods. However, it is believed that there is too large a variability to allow purely manual application of testing exercise to be as effective as machine applied and machine assisted exercises.

An aspect of some embodiments of the invention relates to monitoring brain activity to determining if a physical rehabilitation activity is having a desired effect in the brain. In an exemplary embodiment of the invention, the brain measurements are used as feedback to a patient to indicate if the patient is applying a correct concentration or directed effort. Failure by the patient may suggest the use of other exercises. In one example, if it is clear that the patient is expending effort on a wrong activity, a new exercise where the wrong activity is minimized (e.g., power boosting of motions) may be provided. In another example, complex exercises may be simplified to the point where a patient is able to achieve correct (or progressing) brain activation.

In an exemplary embodiment of the invention, monitoring of brain activity is used to detect restoration of a correct balancing of brain activation. In some cases, such balancing is not possible due to organic damage. However, an expected degree of balancing (e.g., based on an assessment of damaged tissue) can be aimed for. In other cases, a similar activation across a range of exercises is a target.

In an exemplary embodiment of the invention, the characteristics of the movement, (for instance free, synchronized or syncopated) and/or the presence or absence of pre warning cue, (promoting a CNV type of response), may determine the degree of contra-lateral spread of the MAC signal over the scalp. In an exemplary embodiment of the invention, this may be used intentionally to have a desired effect. Alternatively or additionally, this may be measured to determine if a desired effect was achieved.

An aspect of some embodiments of the invention relates to the support of cognitive activities by a physical system. Optionally, such support allows a patient to focus his energies and/or attention on damaged brain areas, reduce fatigue and/or enable the execution of otherwise too complex exercise. In an exemplary embodiment of the invention, cognitive support is provided by one or more of visual feedback or anticipatory display (e.g., a 3D movie), audio feedback, kinesthetic feedback from the same or other arm (e.g., by moving the arm before the exercise or by applying an external force to aid in recognizing when the arm is off-line), providing a power boost so patient is not required to concentrate on details of

carrying out and/or correcting the motion, exemplifying complex motions so less memory is needed to recall and/or understand such motions and/or assisting in overcoming pain, for example by allowing patient to feel the pain ahead of time or by reducing muscle activity of the patient and thus pain.

An aspect of some embodiments of the invention relates to replacing brain functions by a physical manipulation system. In an exemplary embodiment of the invention, kinesthetic feedback analysis is augment or replaced by a manipulation system providing such feedback and/or closing the correctional loop of the motion. Alternatively or additionally, other activities, such as planning are provided by the system.

An aspect of some embodiments of the invention is to provide encouragement during rehabilitation, for example, indicating one or both of correct (or progressive) brain activity and motion. Optionally, provision of a power boost to an existing weak motion and/or augmenting positional feedback and/or reducing the complexity of motion can be used to encourage a patient additionally or alternatively to them being used to assist in the cognitive aspects of rehabilitation.

An aspect of some embodiments of the invention relates to ensuring a correct mental imagery by a patient by actually carrying out the motion or a similar motion for the patient. In some cases, damage to the brain may make such imaging difficult or impossible. In other cases, it is not clear if the patient correctly understood instructions. In an exemplary embodiment of the invention, the presented motion can then be compared exactly to an actually carried out motion. In this and other embodiments of the invention, a robotic manipulator may be replaced by one or more position and/or orientation sensing devices and having a human move the patient and the motion be tracked by the position sensing device. However, an advantage of a robotic manipulator is being able to define ahead of time what the motion or motion response will be, which may not be as precise with a human manipulator.

An aspect of some embodiments of the invention relates to using a robotic manipulator to provide incorrect or partial motions. In one example, the robotic manipulator applies force which is contrary to a motion planned by a patient. This may be used, for example for assessment, by measuring the patient response, or as training to overcome obstacle or train certain brain areas. In another example, a robotic manipulator starts a motion and then becomes passive, or less active, to see if the patient can compensate or complete a motion on its own. In another example, the manipulator can be used to allow a patient (or therapist) to plan motion and/or make changes in planned motions, so that the patient can experience

motions and cognitive activates not otherwise possible. Optionally, after such palling, the motion is executed or the patient is assisted with the motion. Optionally, a graphical interface is used for such planning or changing. Alternatively or additionally, a physical interface, of the manipulator making a motion or a patient moving the manipulator, is used as an input. Optionally, brain activity during such planning is also measured and optionally shown to the patient (directly or simplified) as feedback or to show progress in planning ability.

An aspect of some embodiments of the invention relates to assessing readiness. In an exemplary embodiment of the invention, a patient uses a manual input to indicate readiness for an exercise (e.g., that planning is completed). In an alternative embodiment, brain activity analysis is used for such assessment. In one example, imposed motion is applied at a time when the patient is ready for it. In one example, brain signal processing indicates such readiness, as described in the background. In another example, various delays relative to such calculated readiness are tried out for a patient and/or for various types of motion. In another example, brain signal analysis is used to assess when attention is properly focused. Optionally, such analysis is used as feedback for training the patient in attention and/or to assist a patient in detecting when such attention is lacking.

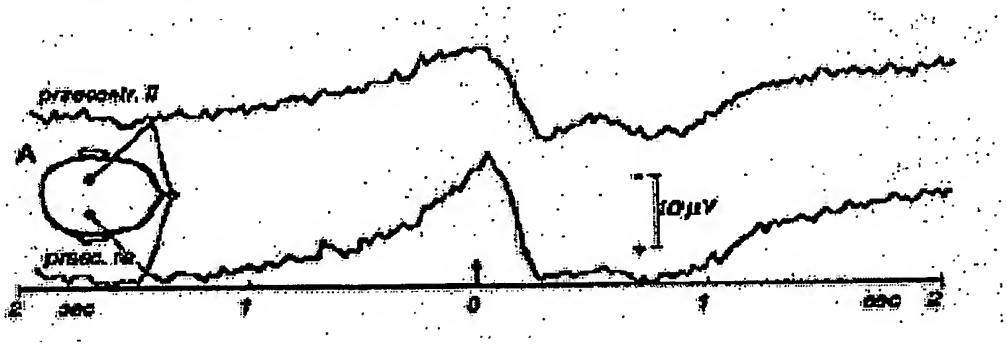
In an exemplary embodiment of the invention, in addition to or instead of contra lateral stimulation of muscles in a paretic arm, MAC slow waves recorded as a result of well defined movement procedure (e.g., organized and delivered by a robot manipulator) are optionally used as markers of attention and optionally as promoters of plasticity and rehabilitation.

An aspect of some embodiments of the invention relates to assessment of rehabilitation time and/or type. In an exemplary embodiment of the invention, a baseline is set for one or both of motion ability and cortical electrical activity. The performance of a patient is compared to one or both baselines, for example to determine a rehabilitation stage, rehabilitation block (e.g., certain brain area not progressing) or a progress rate. In an exemplary embodiment of the invention, the baseline is set by the same patient for a healthy limb. Alternatively or additionally, the baseline is set by a healthy person. In an exemplary embodiment of the invention, a patient is compared to progress and measurements of other patients with similar healthy brain scans (e.g., for unimpaired motion) and/or patients with similar organic damage.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Recording setup

Figure 6 shows a proposed recording arrangement to monitor MAC and the expected signals related to a left arm movement (deeper BP and higher MP recorded over the right hemisphere). Note that (unlike previous Figures) here negative deflection is upwards.



A device utilizing Robot manipulation (hereafter also termed "Armstrong") with MAC and methodology therefore can be applied in various different ways depending on the degree of paresis and the purpose of the exercise.

At certain stages there may be a desire to work on a single arm at a time; sometimes both arms are used together in a mirror like fashion and sometime are used alternatively one after the other.

Likewise, sometimes a single movement is repeated again and again and in others, two or more movements. For instance it may be necessary to establish a schedule by which an "easy" movement is followed by a "difficult" one to encourage further plasticity after some rehabilitation gain has been established.

In an exemplary embodiment of the invention, a "personal signature" of parameters for movement, associated MAC and coexisting sEMG will be established for a healthy arm and even in some cases bilaterally for totally healthy individuals. These are optionally used as standards against which performance of paretic arms during the rehabilitation process are compared and/or assessed, qualitatively and/or quantitatively.

Below we will describe two rehabilitation clinical paradigms to be used with the Armstrong + MAC system together with the algorithmic analysis proposed to monitor, quantify and assess performance and progress.

Calculation of Bilateral Cortical Activation

The first exercise requires the synchronized bilateral movement of arms, (paretic and healthy), in a mirror like fashion; so that the same set of bilateral homologous muscles are activated in the same progressive fashion along the movement path.

During each cycle (movement loop) and for each one of the peripheral muscles monitored by the sEMG facility, (a four muscle sEMG arrangement described above) "Armstrong" performs/displays the following methodological/processing stages, with the caveat that the particular numbers shown are only intended to be examples:

1. Upon each start of each movement loop, display a special audio-visual stimulus that acts as t0 synchronization cue of the movement loop. At t0 all data is refreshed and Armstrong internal clock starts to count.

2. Record continuously a self-refreshing time series of pre-filtered and smoothed (using suitable moving average) slow cortical data (recorded from electrodes C3 and C4) over X1=500 msec (X1 variable could be changed according to experimental adjustment). This array of data has a length that can cover the late part of BP (BP2) and the beginning of the muscular activation (MP). (See Figure 1.). The sequence of data in each MAC signal between BP2 and MP shows a sudden shift from maximal negativity at the end of BP2 to maximal positivity after the muscle starts to contract. We propose to exploit this particular striking feature of every MAC for detection and quantification purposes. In the conventional experimental approach to MAC the investigators are rather interested in the actual shape of the MAC particularly over the degree of negativity of the BP and CNV. In order to improve signal to noise ratio they follow a summation and averaging process over repeated similar signals/trials so that noise cancels out and a cleaner averaged signal emerges from the process. In this embodiment, we attempt to extract reliable data from a single trial and therefore we concentrate on the BP2-MP transition shift that, possibly provides the means to execute quantification/biofeedback steps for every single muscle contraction of a single trial.

3. Identify the onset of the sEMG on the healthy side as trigger (TM).

4. Store time of TM (t1) in the internal clock.

5. Calculate the delay to contraction (D= t1-t0) and compare with expected value (from previous loops and "personal signature"). Each one of the agonist/antagonist muscles involved sequentially in a fixed (in time and space) movement will have its own characteristic time of contraction; therefore, the series of Ds over each movement loop can serve as a measure of the synchronization control of the movement as a whole.

6. Upon monitoring TM, (for each muscle), calculate the differential values from the data present in the self-refreshing time series data array recorded continuously (see stage 2.). Store discreet differential values for a period from 250 msec before TM until 250 msec after TM (DIFF TM). Here the marked deflection between the largely negative late BP2 stage and the largely positive early MP stage gives a series of differential values with a positive spike-like peak shape over this phase of the MAC.

7. Establish maximum value of DIFF TM (DIFF TM Max). This event should generally take place immediately after the start of muscular contraction t1.

8. Calculate and store time of DIFF TM Max (t2)

9. Calculate t2-t1 = SYNC. Values of SYNC < 0 and > 50 msec are possibly erroneous and may indicate bad synchronization between cortex activation and motor performance or may be an artifact. SYNC is therefore a self-testing parameter.

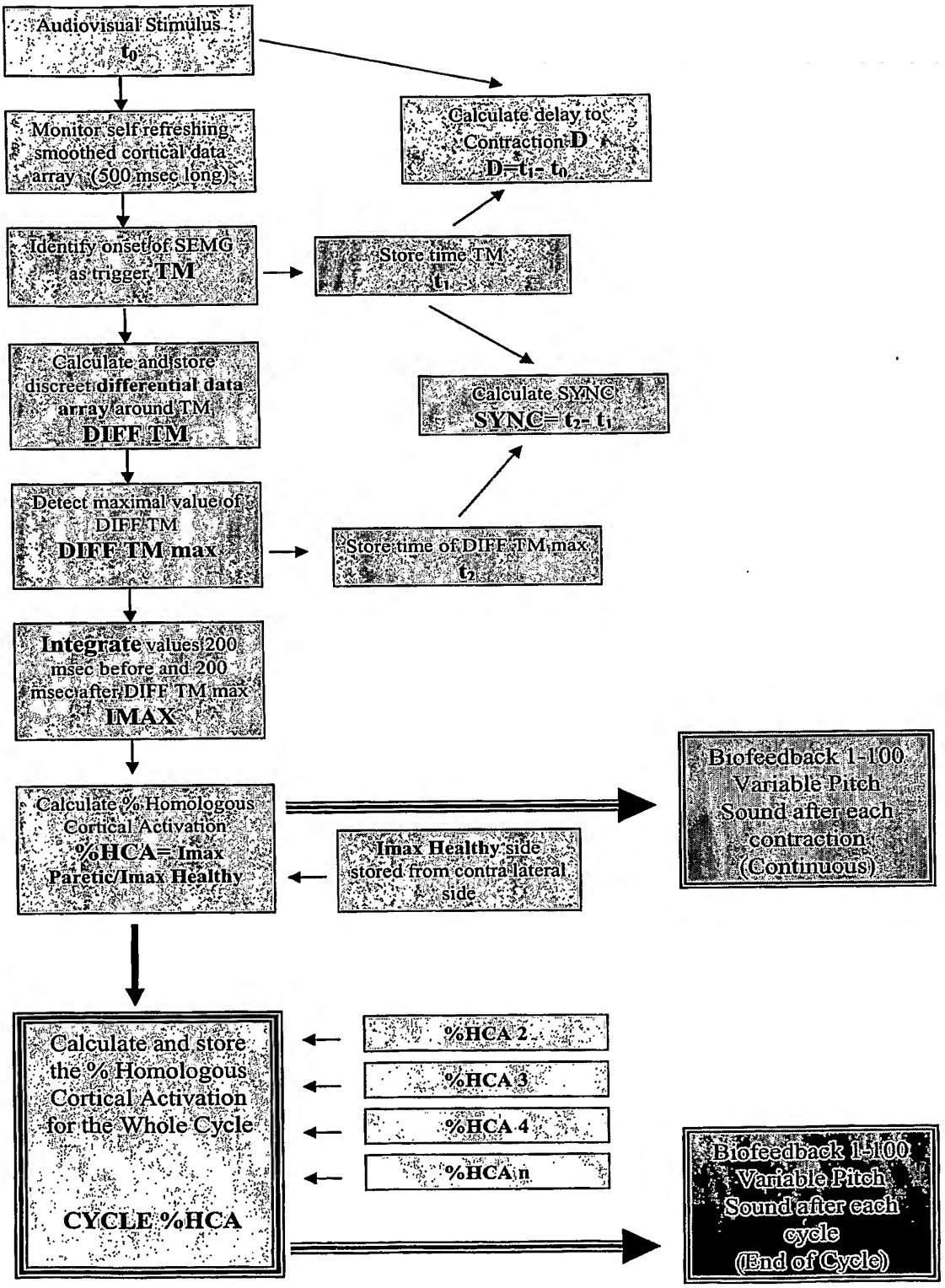
10. Integrate (mean) values for 400 msec ; 200 msec before and 200 msec after DIFF TM Max (Imax) and store this bit of data for each muscle bilaterally. The window of differential data to be integrated is "trimmed" from 500 msec in previous stages to 400 msec in order to avoid the influence of semi-raw data above, (before) the maximal negativity point during BP2 or data below, (after), the maximal positivity point during MP.

11. Calculate Imax Paretic / Imax Healthy * 100 = %HCA (% of Homologous Cortical Activation) for each part of Homologous muscles in the upper arm. %HCA provides an immediate value for the degree of activation opposite to the paretic side in relation to the healthy control.

12. %HCA is translated into suitable 1-100 variable pitch sound delivered at the end of each contraction of each muscle as audio feedback to patient. Since it can be important to provide accurate on-line biofeedback there is optionally provided a "safety valve" that will prevent the display of erroneous biofeedback: Audio biofeedback results are displayed, and % HCA are stored for subsequent post-processing only if SYNC < 0 and > 50 and D is as expected from personal signature (see sections 5. and 9. above). The series of audio displays, (one after each muscle contraction), described in this section represents a form of continuous audio biofeedback along the movement loop. This feature may enable the user to identify particularly difficult stretches along the path. Only when a continuous series of high pitch sounds are heard all through the loop the user realize that that particular movement has been totally "conquered".

13. Upon the completion of each Armstrong cycle, calculate mean values of % HCA for all muscles during the loop (CYCLE % HCA). Store CYCLE % HCA for each loop and sound a rather longer 1-100 variable pitch sound which represent the sound feedback for the whole cycle. In this way the user can be provided with online continues feedback, feedback at the end of each cycle and/or an assessment feedback value at the end of a series of cycles at the end of a rehabilitation session.

This process is also shown in the flowchart below.



Calculation of Mono-lateral Cortical Activation

The second exercise involves the work with a single paretic arm. In this embodiment the methodology/processing is similar to the one describe previously but the results are compared with those of a trial completed previously with the healthy contra lateral arm.

If the patient is unable to carry out the exercise loop with the strength of his own muscles Armstrong may become active and move the arm (totally or just partially adding its force to the one generated by the subject). The triggering schedule in this case is also provided by Armstrong using pre-programmed time cues calculated from the patient signature with the healthy arm in previous trials.

A paradigm as the one just described follows a format similar to the S1-S2 paradigm used experimentally to study CNV (see background).

An example of an experiment follows, again, with the numbers being exemplary only:

1. Before the start of each movement loop, display a special audio-visual stimulus (**S1**) that acts as t0 synchronization cue of the movement loop. At t0 all data is refreshed and Armstrong internal clock starts to count. For this type of exercise the user is instructed that after t0 s/he will be asked to contract a muscle and start a movement by displaying a second time cue t1 (described in 3.)
2. Record continuously a self-refreshing time series of pre-filtered and smoothed (using suitable moving average) slow cortical data (recorded from electrode over the contra lateral central zone; C3 or C4) over X1=500 msec (X1 variable could be changed according to experimental adjustment).
3. Relate to a time (t1) for the contraction of a particular muscle. (This time has been previously calculated for the healthy arm). At this stage Armstrong provides another time cue (**S2**) signaling the start of the contraction.
4. Calculate the differential values from the data present in the self-refreshing time series data array recorded continuously (see stage 2.). Store discreet differential values for a period from 250 msec before S2 until 250 msec after S2 (**DIFF S2**).
5. Establish maximum value of DIFF S2 (DIFF S2 Max). This event should generally take place immediately after the start of muscular contraction t1.
6. Integrate (mean) values for 400 msec ; 200 msec before and 200 msec after DIFF S2 Max (Imax) and store this bit of data for each muscle.
7. Calculate Imax Paretic / Imax Healthy (previously recorded) * 100 = %HCA (% of Homologous Cortical Activation) for each part of Homologous muscles in the upper arm.

8. %HCA is translated into suitable 1-100 variable pitch sound delivered at the end of each contraction of each muscle as audio feedback to patient.

Upon the completion of each Armstrong cycle, calculate mean values of % HCA for all muscles during the loop (CYCLE % HCA).

Activation of Damaged side of Cortex from healthy contra lateral BP

In an exemplary embodiment of the invention, another mode of operation of the proposed system is essentially the detection and use of a BP2-MP time cue from the healthy side, (as described above), in order to stimulate the contra lateral, (damaged side), of the cortex with an electromagnetic coil similar to the ones used in conventional EM Cortex Stimulation. Alternatively or additionally, stimulation is provided by using Armstrong to move the paretic limb.

This embodiment represents a kind of FES (Functional Electro Stimulation) that is based on the activation of the contra-lateral healthy side while performing a bimanual mirror like type of movement as described in Section 4.1

In an exemplary embodiment of the invention, what is desired is not to provoke a contraction but just to stimulate below the threshold of contraction so as to assist any endogenous production of MP to achieve over-threshold values and be effective in order to produce movement. This particular arrangement may help the user also to associate central activation with peripheral movement, hence encouraging plasticity. Optionally, actual motion is also helped by Armstrong, possibly further reducing the threshold.

Alternatively or additionally to electromagnetic or electrical stimulation (e.g., using a DC current), in an exemplary embodiment of the invention, mental imagery or other cognitive activity caused by the manipulation system has an effect of activation. Optionally, the assistance of the manipulation system acts to lower the threshold, rather than to activate. Optionally, the assistance of the manipulation system acts to reduce mental concentration required for planning the details of the motion and/or performing real-time feedback to ensure the motion is correct and, instead, a patient is freer to concentrate on planning of the motion. In an opposite usage, the fact that the manipulation system moves the limb allows a patient to clearly mentally image the motion, so the planning stage is made easier, leaving more attention to other stages.

In one example, assistance is by the system providing a power boost to motions provided by the patient. In another example, assistance is by the system applying a force that returns the limb to the correct path (e.g., instead of or in addition to such force applied by the patient). In

another example, assistance is by the system moving the limb through the required motion, to help create suitable mental imagery or learn the expected kinesthetic feedback. Similarly, a patient, by such assisted motion, can learn when to expect pain, or which parts of the motion might require more concentration and/or planning. In another example, the system provides the tempo of the motion (e.g., velocity amplitude) with the patient providing direction, or vice-versa. In another example, the system repeats a motion carried out by the patient with the same or opposite limb, allowing the patient to "merely" repeat a pervious planning or execution activity.

The system optionally provides a score during such a pre-test, showing the patient where more effort will be required during voluntary motion. Alternatively or additionally, as noted above, such feedback can be provided during motion, for example to assist in attention.

Various designs for robots and positioning devices (e.g., hexapods) are known in the art. It should be appreciated that various ones of the statements described herein may be adapted for such robots and/or positioning devices, in accordance with exemplary embodiments of the invention. Alternatively or additionally, software may be provided for such robots and devices for carrying out various of the methods described herein, all in accordance with exemplary embodiments of the invention.

In some embodiments of the invention, the systems described herein are used for uses other than rehabilitation, for example, task training, testing and/or robotic manipulation.

It will be appreciated that the above described methods of rehabilitation may be varied in many ways, including, omitting or adding steps, changing the order of steps and the types of devices used. In addition, a multiplicity of various features, both of method and of devices have been described. In some embodiments mainly methods are described, however, also apparatus adapted for performing the methods are considered to be within the scope of the invention. It should be appreciated that different features may be combined in different ways. In particular, not all the features shown above in a particular embodiment are necessary in every similar embodiment of the invention. Further, combinations of the above features are also considered to be within the scope of some embodiments of the invention. Also within the scope of the invention are kits which include sets of a device, one or more limb holding attachments and/or software. Also, within the scope is hardware, software and computer readable-media including such software which is used for carrying out and/or guiding the steps described herein, such as control of arm position and providing feedback. Section headings are provided for assistance in navigation and should not be considered as necessarily limiting the

contents of the section. When used in the following claims, the terms "comprises", "includes", "have" and their conjugates mean "including but not limited to". It should also be noted that the device is suitable for both males and female, with male pronouns being used for convenience.

It will be appreciated by a person skilled in the art that the present invention is not limited by what has thus far been described. Rather, the scope of the present invention is limited only by the following claims.

CLAIMS

1. A method of rehabilitation, comprising:

attaching a paretic limb of a patient to a robotic manipulator;

measuring EEG activity of a brain of the patient; and

determining a desired action of said robotic manipulator on said paretic limb responsive to said measuring.

2. A method according to claim 1, wherein said measuring comprises measuring responsive to a movement of a healthy limb of said patient.

3. A method according to claim 1, wherein said measuring comprises measuring responsive to instructions given to the patient.

4. A method of rehabilitation, comprising:

attaching a paretic limb of a patient to a robotic manipulator;

performing a desired action of said robotic manipulator on said paretic limb ; and

measuring EEG activity of a brain of the patient responsive to said action.

5. A method according to claim 4, comprising determining a rehabilitation step responsive to a result of said measuring.